

REMARKS/ARGUMENTS

In response to the pending Office Action of April 20, 2004, Applicants present the following arguments and claim amendments. The present amendments are requested to more clearly claim the present invention do not introduce any new matter. Applicants submit that in light of the arguments presented and amendments requested this application is in condition for allowance. Therefore, reconsideration and withdrawal of all the pending rejections is respectfully requested.

A Request for Continued Examination, Petition for Two Month Extension of Time and the required fees are provided with this response. With the entry of this amendment, claims 31, 33-35, 61, 64, 68, 71, 73 – 76 and 80 - 85 are pending herein.

Examiner Interview and Request for Information

Examiner Lauren Q. Wells, Examiner Gregory W. Mitchell and Supervisor Examiner Sreeni Padmanabhan are thanked for their valuable participation in a telephone interview on August 5, 2004. Pursuant to MPEP Section 713.04, a summary of this interview was submitted to the U.S. Patent and Trademark Office on September 3, 2004.

Amendments

Amendments of claims 31, 80, 81 and 82 are requested to more particularly point out and distinctly claim the present invention. Amended claims 31, 80, 81 and 82 now recite "wherein said particles bind directly to said fibrin." In addition, new claims 84 and 85 have been added which depend from amended claim 31 and recite the additional limitations "wherein said graphitic carbon outer surface of said particles directly binds to said fibrin" and "wherein said particles selectively bind to said fibrin," respectively. Support for the requested

amendments and new claims is provided by the teaching on page 10, lines 10 - 12 that diagnostic particles of the present invention exhibit "specific affinity" for fibrin. In addition, support for this amendment is provided by the experimental results presented in Examples 3 - 7, which demonstrate that the diagnostic particles of the present invention exhibit "specific binding capacity for fibrin" without surface derivatization or use of surfactants. (page 14, line 20 to page 16, line 9). The requested amendments do not introduce any new matter.

Amendments of claims 31, 80, 81 and 82 are also request to delete the recitation "allows for a stable chemical association with an aqueous medium." During the telephone interview of August 5, 2004, the Examiner expressed concern that the term "stable chemical association" in these claims may be unclear. Applicants respectfully disagree with the Examiner's conclusions regarding the clarity of this claim language. To expedite prosecution and without acquiescing to the Examiner's characterization, however, this language has been deleted from amended claims 31, 80, 81 and 82. The requested amendments do not introduce any new matter.

Amendment of claims 80 and 81 is requested to change the recitation "at least two" to recite "about 2 to 20." Support for the requested amendment is provided in the description of a preferred embodiment wherein "the detectable marker is preferably encased in about 2 to 20 layers of graphitic carbon" on page 4, lines 3 - 6. The requested amendments do not introduce any new matter.

Rejections under 35 U.S.C. § 103

Claims 31, 33-34, 61, 71 and 80 - 83 have been rejected under Section 103(a) as allegedly unpatentable over International Patent Application No. WO93/15768 (Watson *et al.*) in view of The handbook of Carbon, Graphite, Diamond and Fullerenes and in view of U.S. Patent No. 5,217,705 (Reno *et al.*). In support of this rejection, the Examiner characterizes Watson *et al.* as teaching "the use of macromolecular compounds having tight molecular meshes, such as

graphite carbons, in diagnostic and/or therapeutic agents, especially diagnostic imaging contrast agents,” The Handbook of Carbon, Graphite, Diamond, and Fullerenes as teaching “graphite crystal as being in the form of multiple layers” and Reno as teaching “a method of diagnosing blood clots using fibrin-binding proteins.” With respect to the combined teaching of these references, the Examiner concludes that:

[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to teach the graphitic carbon as comprising two or more layers because the The Handbook of Carbon, Graphite, Diamond, and Fullerenes teaches graphitic carbon as being in the form of multiple layers . . . it would have been obvious to one of ordinary skill in the art at the time of the invention was made to exemplify graphitic carbon in substitution for fullerenes in the examples of Watson because Watson teaches graphitic carbon and fullerenes as interchangeable macromolecular compounds . . . [and] it would have been obvious to one of ordinary skill in the art at the time the invention was made to teach fibrin-binding proteins, as taught by Reno et al., as the proteins of Watson et al. because Watson et al. teach their agents for targeting the blood pool and because of the expectation of achieving a stable contrast agent that is able to locate harmful fibrin blood clots.”

Applicants respectfully traverse these rejections. Amendment of the rejected claims is requested, however, to more clearly specify the claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the rejections in light of the following arguments.

First, the inventions of rejected claims 31, 33-34, 61, 71 and 80 – 83 are directed to methods for detecting fibrin which utilize administration and detection of diagnostic carbonaceous particles capable of forming a colloid upon dispersal into an aqueous medium and capable of binding to fibrin. Applicants show that the diagnostic carbonaceous particles of the present invention exhibit high affinity and specific binding affinity for fibrin in a variety of experimental conditions, including *in vivo* conditions, and believe that they are the first ones to identify these properties and use them in the methods of the present invention. (See e.g.,

pg. 2, lines 17 – 20 & Examples 3 – 27, pages 14 – 26). The high binding affinity and selectivity to fibrin of the diagnostic particles of the present invention are significant features of the present methods because these characteristics provide for accurate, sensitive and selective labeling of fibrin which serves the basis of important diagnostic procedures and therapies relating to the detection and treatment of disease.

Claims 31, 33-34, 61, 71 and 80 – 83 are not rendered obvious by the cited combination of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.* because these references do not disclose or even suggest the specific binding of the carbonaceous particles of the present invention to fibrin which serves the basis of the step of “binding said diagnostic particles to said fibrin” in the rejected claims. First, Watson *et al.* provides a generic teaching of the use of non-diamond carbon allotropes as therapeutic agents. However, nowhere in this reference is the capability of carbonaceous particles, such as graphitic carbon particles, to bind to fibrin mentioned or suggested, let alone is the selectivity and high affinity of this interaction described. Second, Reno *et al.* provide methods of detecting fibrin under *in vivo* conditions. Although the methods provided by Reno *et al.* also utilize a diagnostic agent capable of selectively binding to fibrin, the scope of the disclose in this reference is limited to the use of thrombolytic proteins, such as plasmin and plasminogen activators, rather than carbonaceous particles. Third, The Handbook of Carbon, Graphite, Diamond, and Fullerenes provides a summary of the chemical properties and reactivity of graphite. The summary provided, however, fails to disclose or suggest the possibility of selective reactivity of particles comprising graphitic carbon with fibrin. Rather, this reference characterizes graphite as “one of the most chemically inert materials,” further reinforcing the surprising and nonobvious nature of the selective binding interaction between carbonaceous particles and fibrin that serves the basis of the methods of the rejected claims. (Section 7.1, pg. 63 of The Handbook of Carbon, Graphite, Diamond, and Fullerenes)

Moreover, with respect to claims 82 and 83, Applicants note that the references relied upon by the Examiner do not disclose the limitation "wherein said particles are made by heating a carbon crucible having deposited thereon a detectable marker to a temperature in the range of about 2250° C to about 3000° C in an inert gas and in a sealed container, thereby generating particles suspended in said inert gas, precipitating said particles suspended in said inert gas to form said diagnostic particles." Rather, the cumulative teaching of these references provides no instruction related to any methods of preparing graphitic carbon particulate, let alone the method expressly recited in claim 82 and does not disclose carbonaceous particles having an equivalent composition to particles generated by the method specified in claim 82. Therefore, claims 82 and 83 are not rendered obvious by the cited combination of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.* because these references do not disclose or suggest all the limitations in the rejected claims.

To clarify important distinctions between the methods of the rejected claims and the combined teaching in of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.*, rejected claims 31, 33-34, 61, 71 and 80 – 83 are amended to recite the limitation "wherein said particles bind directly to said fibrin." Further, claims 80 and 81 have been amended to recite the limitation of "about 2 to 20 layers of carbon." Applicants submit that this additional claim language distinguishes the methods of the amended claims from methods wherein reactivity with fibrin is provided by derivatization of the surface of carbonaceous particles via incorporation of fibrin binding proteins, as proposed in the pending Office Action. As Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.*, taken individually or in combination, do not disclose or suggest all the limitations in the rejected claims, and the missing claim limitations are well outside the grasp of the

typical artisan at the time of invention, it is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection. See, e.g., In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Second, Applicants submit that the Examiner improperly relies on the inherency of a characteristic of Applicants' diagnostic particles that was not known or even suggested at the time of the invention. Applicants disagree with the Examiner's conclusion that:

[a]ny properties exhibited by or benefits provided [by] the composition are inherent and are not given patentable weight over the prior art . . . [a] chemical composition and its properties are inseparable . . . [t]herefore, if the prior art teaches the identical chemical structure, the properties Applicant discloses and/or claims are necessarily present. (citing In re Spada, 911 F.2d 705, 709, 15 USPQ2D 1655, 1658 (Fed. Cir. 1990).

Applicants respectfully point out that the holding in In re Spada relates to an anticipation rejection under 35 U.S.C. § 102 ("we conclude that the Board correctly found that the virtual identity of monomers and procedures sufficed to support a *prima facie* case of unpatentability of Spada's polymer latexes for lack of **novelty**." In re Spada, 911 F.2d 705, 709, 15 USPQ2D 1655, 1658 (Fed. Cir. 1990), emphasis added). In contrast, the pending rejections of claims 31, 33-34, 61, 71 and 80 – 83 are made under 35 U.S.C. § 103(a). In the context of an obviousness rejection under § 103, the Federal Courts have long held that "the inherency of an advantage and its obviousness are entirely different questions. . . [o]bviousness cannot be predicated on what is unknown." In re Sporman, 150 USPQ 449, 452 (CCPA 1996). As applied to the present case, Applicants submit that the chemical property of the diagnostic particles of rejected claims 31, 33-34, 61, 71 and 80 – 83 to selectively bind to fibrin was not known or even suggested at the time of the invention, and therefore, the Examiner may not properly rely on the inherency of this unknown and nonobvious characteristic to support the present nonobviousness rejection under 35 U.S.C. 103(a). Accordingly, Applicants submit that no *prima facie* case of nonobviousness has been made

out with respect to this rejection, and thus, reconsideration and withdrawal are respectfully requested.

Further, Applicant disagree with the Examiner's characterization that:

the prior art teaches administration to a patient of compositions containing the same components as instantly claimed, which would inherently detect fibrin in the blood stream or blood vessel as instantly claim.

Contrary to this characterization, Applicants submit that none of the prior art references cited in the present rejections disclose administration of particles have the same composition as the diagnostic particles of the present invention into the blood stream or into a blood vessel. Further, applicants submit that even if the composition of diagnostic particles of the rejected claims was known at the time of the invention, the present claims are patentable as "a new use of a known . . . composition of matter." See *e.g.*, 35 U.S.C. §§ 100(b), 101, Saes Getters S.P.A. v. Ergenics Inc., 17 USPQ2d 1581, 1586 (D.N.J. 1990) (holding "a process using [the prior art alloy] in a new and unobvious way may be patentable"); citing Loctite Corp. v. Ultraseal Ltd., 228 USPQ 90, 99 (Fed. Cir. 1985); In re Schoenwald, 22 USPQ2d 1671, 1673 (Fed. Cir. 1992) (recognizing a method claim for ophthalmic compositions to treat dry eye syndrome, but not a product claim to the composition, is allowable when a new use is discovered for a composition known to the art). Accordingly, reconsideration and withdrawal of the pending rejections is respectfully requested.

Third, claims 31, 33-34, 61, 71 and 80 – 83 are not rendered obvious because the combined teachings of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.* do not enable synthesis of the compositions relied upon by the Examiner in the pending rejections. In support of the pending Office Action, the Examiner asserts that the combination of Watson *et al.* and Reno *et al.* teach graphite surfaces modified to have

biologically active, surface bound, fibrin-binding proteins. Contrary to the Examiner's conclusion that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to teach fibrin-binding proteins, as taught by Reno *et al.*, as the proteins of Watson *et al.*," Applicants submit that the cumulative teaching of these references do not enable synthesis of graphite surfaces having biologically active, surface bound fibrin binding proteins. As taught in The Handbook of Carbon, Graphite, Diamond, and Fullerenes, graphite is an extremely stable material. Therefore, derivatization of graphite surfaces is likely to involve complex chemical addition reactions proceeding under well defined, specific reaction conditions. However, there is no teaching in Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes or Reno *et al.* providing a chemical mechanism for coupling fibrin binding proteins to highly inert graphite surfaces. Indeed, neither Reno *et al.* nor Watson *et al.* even suggests incorporation of fibrin binding proteins to carbonaceous materials. References which do not enable one skilled in the art to construct and practice a claimed invention are not properly cited as prior art. See, e.g., In re Hoeksema, 158 U.S.P.Q. 596, 600-01 (CCPA 1968). It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

Fourth, the Examiner does not provide a credible motivation to combine the teachings of teachings of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.*, and the combined teaching of these references does not provide a reasonable expectation of successfully arriving at the methods of detecting fibrin of the rejected claims. The Examiner indicates that it would have been obvious to one of ordinary skill in the art to modify the graphitic surfaces of Watson *et al.* to incorporate the fibrin-binding proteins of Reno *et al.* However, The Handbook of Carbon, Graphite, Diamond, and Fullerenes, also relied upon by the Examiner in the pending rejections, characterizes graphite as "one of the most chemically inert materials." (Section 7.1, pg. 63 of The Handbook of Carbon, Graphite, Diamond, and Fullerenes)

Given this characterization of the reactivity of graphite, it is unlike that a person of ordinary skill in the art would be motivated to attempt to derivatize the extremely inert graphitic surfaces of Watson *et al.* to incorporate the fibrin-binding proteins of Reno *et al.* Nor is it likely that the skilled artisan would have a reasonable expectation of successfully achieving the composition relied upon by the Examiner in the present rejections because a person of ordinary skill in the art would not expect that fibrin binding proteins can be chemically coupled to inert carbon surfaces, such as graphitic carbon surfaces, without affecting the protein's structure and its ability to selectively bind to fibrin. Proteins are known to readily undergo irreversible conformational changes when their chemical environment is changed and these changes often irreversibly affect their biological activity. References which do not provide a reasonable expectation of successfully practicing the invention as claimed are not properly cited as prior art. See, e.g., Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016, 1022 – 23 (Fed. Cir.), *cert denied*, 502 U.S. 856 (1991). It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

Claims 64 is rejected under Section 103(a) as allegedly unpatentable over Watson *et al.* in view of The Handbook of Carbon, Graphite and Diamond and in view of Reno *et al.* and further in view of the Handbook of Cosmetic Science and Technology. Claim 68 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Watson *et al.* in view of The Handbook of Carbon, Graphite and Diamond and in view of Reno *et al.* and further in view of U.S. Patent 5,330,768 (Park *et al.*) and Penfold *et al.* Claim 35 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Watson *et al.* in view of The Handbook of Carbon, Graphite and Diamond and in view of Reno *et al.* and further in view of U.S. Patent 5,952,321 (Doherty *et al.*). Applicants respectfully traverse these rejections. Amendment of the claims from which rejected claims depend from is requested, however, to more clearly specify the claimed invention. Accordingly,

Applicants request reconsideration and withdrawal of the rejections in light of the following arguments.

The arguments set forth above with respect to claims 31, 33-34, 61, 71 and 80 – 83 are reasserted in the context of the rejections of 64, 68 and 35. The combined teachings of Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al* do not disclose, enable or suggest step of binding the diagnostic particle to fibrin, wherein the diagnostic particles bind directly to fibrin. Moreover, the teaching in Handbook of Cosmetic Science and Technology, Park *et al.*, Penfold *et al.*, or Doherty *et al.* does not supplement the disclosure in Watson *et al.*, The Handbook of Carbon, Graphite, Diamond, and Fullerenes and Reno *et al.* in a manner satisfying these deficiencies. In addition, there is no suggestion or motivation to combine these references and there is not teaching sufficient to enable a person of ordinary skill in the art to integrate these teachings to successfully arrive at the methods 35, 64 and 68. Nor is it likely that the skilled artisan would have a reasonable expectation of successfully combining the diverse teaching of these references in a manner arriving at the methods of the rejected claims. It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to the rejections of claims 64, 68 and 35, and withdrawal of these rejections is respectfully requested.

CONCLUSION

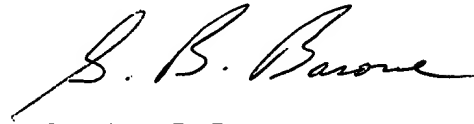
In view of the foregoing arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call and arrange for an opportunity to discuss these issues via phone interview.

It is believed that a two month extension is required with this submission. Therefore, a petition for a two month extension and fee of \$ 440.00 are provided.

Appl. No. 09/463,082
Amdt. Dated September 20, 2004
Reply to Office Action Of April 20, 2004

If this is incorrect, please deduct the appropriate fee for this submission and any extension of time required from Deposit Account No. 07-1969.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "S. B. Barone". The signature is fluid and cursive, with a long horizontal stroke at the end.

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